Cystic fibrosis in South Africa: spectrum of disease and determinants of outcome

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Analysis of the recently established South African CF registry shows that MRSA and undernutrition are associated with severe CF lung disease. Highly effective CFTR modulator therapy would benefit most people with CF. https://bit.ly/2Sf36Vy

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Abstract

Introduction Little is known about cystic fibrosis (CF) in low- to middle-income settings. This study aimed to describe the spectrum and outcomes of CF in South Africa (SA) from the recently established SA CF registry (SACFR).

Methods Demographic, diagnosis and clinical data were extracted from the SACFR. Cross-sectional univariable and multivariable regression analysis of best forced expiratory volume in 1 s (FEV_1; age⩾6 years) and nutrition (all ages) in 2018 was conducted to investigate factors associated with severe lung disease (SLD; FEV_1 ⩽3.0 z-score) and undernutrition.

Results By December 2018, ancestry of 447 individuals included in the SACFR was Caucasian (315; 70%), mixed (87; 19%) and black African (41; 9%). Median diagnosis age was 7.6 months (IQR 2.7–37.1). Genotype was p.Phe508del homozygous (220; 49%); p.Phe508del heterozygous (144; 32%) and neither p.Phe508del or unknown Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) variant in 83 (19%); the second most frequent *CFTR* variant was 3120+1G>A, common in black Africans. Median age of patients in 2018 was 14.7 years (IQR 7.4–24.4). SLD was independently associated with chronic methicillin-resistant *Staphylococcus aureus* (MRSA) (adjusted odds ratio(aOR) 16.75; 95% CI 1.74–161.50), undernutrition (aOR 5.20; 95% CI 2.23–12.13) and age (aOR 2.23 per 10 years; 95% CI 1.50–3.31). Undernutrition was associated in univariable analysis with low weight at diagnosis, non-Caucasian ancestry, chronic *P. aeruginosa* infection and lower socioeconomic status.

Conclusion Interventions targeting MRSA infection and nutrition are needed to improve CF outcomes in SA. Most people with CF in SA are eligible for highly effective CFTR modulator therapy.

Introduction

Cystic fibrosis (CF) occurs with varying frequency in all population groups throughout the world. Although CF survival has improved over the past two decades, it remains a life-shortening condition with a median survival age for a person with CF in 2018 in the United States (US) of approximately 47 years [1]. Nutrition, lung function (LF) and rate of LF decline are important predictors of CF-related morbidity and mortality [2, 3]. Preserving LF and slowing the rate of LF decline is key to improving CF survival.

CF registries from high-income countries have contributed significantly to our understanding of CF epidemiology and survival [4, 5]. Epidemiological and longitudinal data of over 72 000 people living with CF today are currently recorded in CF registries in the US, Canada, Europe, Australasia and Brazil, with coverage rates reported to be as high as 90% of the CF population [5]. Several known modifiable and

non-modifiable factors in high-income countries have been associated with lower LF and accelerated LF decline in CF [6–8]. However, it is unclear if similar or other determinants of CF lung disease exist in low- or middle-income countries (LMIC) such as South Africa (SA). Socioeconomic factors such as poverty, limited access to appropriate healthcare, CF medications and social complexity are more prevalent in LMIC and important factors associated with poor CF-related outcomes such as LF and survival [9–11]. Lower LF and survival has been documented in Hispanic CF populations in the US compared to non-Hispanics [12, 13]. Ancestry and socioeconomic status (SES) are expected to be significant determinants of CF-related outcomes in SA, which is reported to be one of the most unequal societies in the world [14].

South Africa launched its CF registry in 2018 and adopted similar data collection methods as the 2017 European CF registry [15]. South Africa is categorised by the Word Bank as a high- to middle-income country, and it has a population of nearly 60 million [16]. Healthcare infrastructure and services are provided to most of the population through a resource-constrained public health system and a smaller but well-resourced private healthcare system. The prevalence of Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) mutations in the SA population and incidence of CF also varies greatly. P.Phe508del is the most common mutation amongst Caucasians (prevalence 76%), whereas 3120+1G>A is the most common mutation (prevalence 46%) in black Africans [17], with an estimated carrier frequency rate of 1 in 90 healthy individuals [18]. A review of *CFTR* mutations identified across 12 African countries (predominantly Northern Africa and South Africa) identified 70 *CFTR* mutations of which 39 were known disease-causing mutations and five novel mutations [19]. There is therefore an urgent need to investigate the spectrum and determinants of CF disease in the SA population, especially in non-Caucasian people. The aim of this study was to describe the spectrum of CF in SA and explore LF and nutrition outcomes captured in the SA CF registry (SACFR).

Methods

Study design and population

A descriptive cross-sectional study was conducted using anonymised data extracted from the SACFR, a multicentre public–private collaboration designed to collect similar data and variable definitions as per the 2017 European CF patient registry report [20] and SACFR 2018 patient registry report [21]. The SACFR was established in 2018 and enrols consenting adults and children receiving CF care in SA. Recruitment of CF registry participants was initiated through formation of the SACFR steering committee, which represents all known CF care clinics in public and private health sectors. In addition, the SA CF Association, the local CF advocacy organisation, actively promotes participation in the SACFR through its press and social media networks. Data extraction from medical records and data entry into the SACFR is performed by two qualified data managers who visit each participating site on an annual basis. Demographic, CF diagnosis and genotype information were extracted and described for all individuals diagnosed in SA up to the end of December 2018. Annual review data for the period January 1 to December 31, 2018 were extracted, including outcome variables: 1) best documented pre-bronchodilator forced expiratory volume in 1 s (FEV_1); and 2) accompanying weight/height (age 6 years and older), or best weight/height if no LF was recorded. In the event of death, the best recorded measurements in 2018 prior to dying were included in analyses. FEV_1 was reported as z-scores calculated with the Global Lung Initiative (GLI) ethnic-specific reference equations [22]. Severe lung disease (SLD) was defined as FEV_1 z-score $\leqslant 3$ [23]. Undernutrition for the purpose of this study was defined according to age group: World Health Organization (WHO) nutritional reference equation weight-for-height z-score (WHZ) $\leqslant 1$ SD in children <2 years of age; body mass index z-score (BMI $kg \cdot m^{-2}$) $\leqslant 1.0$ in children aged 2–17 years; and BMI <18.5 $kg \cdot m^{-2}$ in adults $\geqslant 18$ years of age.

Modified SACFR CF diagnosis inclusion criteria and SACFR variables

People with a confirmed diagnosis of CF were captured in the SACFR if they met the following modified SA CF diagnostic criteria:

1) Two sweat chloride tests >60 $mmol \cdot L^{-1}$ or sweat conductivity >90 $mmol \cdot L^{-1}$ and clinical features compatible with CF or
2) DNA analysis/genotyping identified two disease-causing *CFTR* mutations as reported at the time in CFTR2 [24] database or
3) sweat chloride $\leqslant 60$ $mmol \cdot L^{-1}$ chloride and both of the following criteria are met: 1) DNA analysis/genotyping identified two disease-causing *CFTR* mutations; and 2) clinical presentation consistent with typical or atypical CF or a CF-related disorder (CFRD) [25]. People diagnosed with a CFRD were included in the SACFR.

Additional variables added to the SACFR included: composite measures of SES (*e.g.* public or private healthcare, reliance on public transport; household amenities and receipt of social welfare grants); other infections including *Haemophilus influenzae*, methicillin-resistant *Staphylococcus aureus* (MRSA),

Aspergillus fumigatus, other fungus/mould species, human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis*. Chronic pulmonary infection with CF pathogens was defined by Modified Leeds criteria [26]. Chronic pulmonary infection status was classified as unknown if less than four respiratory samples were submitted for culture during the year or the infection status of each pathogen could not be established from past medical records.

Standard of CF care in South Africa

Multidisciplinary CF care in the public sector is provided at six CF centres located in tertiary hospitals. Individual practitioners with CF expertise provide CF care in the private sector. Essential CF care and CF medications including pancreatic enzyme replacement therapy (PERT), hypertonic saline, azithromycin and antimicrobials are freely available in the public sector, but expensive CF therapies such as inhaled tobramycin solution, recombinant DNase and organ transplantation are restricted or not available in the public sector. Private health insurance schemes in SA vary considerably in what they reimburse for CF care, ranging from basic care equivalent to the public health sector to comprehensive care that includes reimbursement for inhaled tobramycin solution, recombinant DNase and unlimited CF investigations (*e.g.* sputum cultures), however, often with additional out-of-pocket co-payments by the members. Off-label prescription of inhaled intravenous antibiotic formulations (*e.g.* gentamycin, amikacin and colimycin) for treating *P. aeruginosa* infection is widely practised due to lack of affordable alternatives. Reliable sweat chloride testing or sweat conductivity testing in SA is available only in the main cities, and limited *CFTR* panel testing is available. Newborn screening for CF is not widely performed in SA and CFTR modulator therapy is not available in SA. South African Consensus CF guidelines were published in 2017 with recommendations for appropriate standards of CF care for the SA setting [27].

Statistical analysis

Data preparation and analyses were conducted in R (v3.3.3), using the glm function to fit the regression models. Descriptive statistical tests were reported for the spectrum of clinical features and therapies, using data captured in the SACFR. Reported measures of centrality and spread were guided by whether distributions are approximately normal. Groups of individuals (by ancestry or age) were compared using chi-squared or Fisher's exact (categorical variables), Kruskal–Wallis (medians of continuous variables) or ANOVA (means of continuous variables) tests. Differences in pulmonary therapies by whether SLD occurred were assessed using chi-squared tests; ANOVA was used to compare FEV_1 percentage predicted (% pred) means by age category; and Pearson correlation coefficients were used to relate BMI scores to FEV_1 z-scores.

The primary outcome measure in people aged 6 years and older was LF; and nutrition for all ages the secondary outcome. The frequencies of these binary outcomes were analysed using univariable and multivariable logistic regression models, producing unadjusted and then adjusted odds ratios (aORs) for known or suspected demographic, genotype, socioeconomic, nutritional, microbiological and comorbidity/complication risk/protective factors. To reduce the limitations posed by multiple factors considered in testing, we produced adjusted p-values for the unadjusted ORs, using Holm's method. All factors in univariable analysis with unadjusted p-values <0.2 are presented in tables 1–4. Variables with Holms-adjusted p-values <0.2 in univariable analyses were included in the multivariable models, as well as the confounder age. A p-value of <0.05 was considered statistically significant.

This study aligns with the Declaration of Helsinki 2013 and was approved by the Faculty of Health Sciences Human Research Ethics Committee, UCT (HREC R007/2018) and the SACFR steering committee.

Results

Demographic and clinical characteristics at time of CF diagnosis, December 2018)

By 31 December 2018, 447 individuals (235, 52.6% female) with confirmed CF diagnosis were captured in the SACFR. Twelve individuals were excluded from the study as diagnostic criteria of the SACFR were not met and one patient declined registry consent. Median age of diagnosis was 7.6 months (IQR 2.7–37.1), with 253 (56.6%) diagnosed under 1 year of age. Sixty-eight (15.2%) presented with neonatal bowel obstruction (any form of meconium ileus presentation diagnosed clinically and managed operatively or non-operatively), the rest were diagnosed based on symptoms or an affected sibling. Only one child whose family immigrated to SA was diagnosed in the US through newborn screening. Weight and height measurement at diagnosis was missing for 131 (31.3%) and 183 (43.7%), respectively, of 419 children diagnosed aged <18 years. The median weight-for-age z-score (WAZ) of children at diagnosis was −2.2 (IQR −3.8 to −0.9) of which 37.2% were severely underweight for age (WAZ ⩽3.0). Median WAZ differed significantly by ancestry ($p<0.001$) and was lower in non-Caucasian groups (−4.2 to −2.8) than Caucasians (−1.5). One hundred and eighteen (26%) patients had one sweat chloride test and 94 (23%) two; 68 (15%) had one sweat conductivity test and 34 (8%) two. At least one sweat chloride test and/or

TABLE 1 Demographic and clinical information, at time of diagnosis, among the cystic fibrosis population in South Africa, December 2018[#], stratified by ancestry

	Caucasian	Mixed	Black African	Indian	Total
Subjects n*	315	87	41	4	447
Female sex n (%)	179 (56.8)	40 (46.0)	15 (36.6)	1 (25.0)	235 (52.6)
Diagnosis age	**n=309**	**n=87**	**n=39**	**n=4**	**n=439**
Diagnosis age in months, median (IQR)	8.9 (2.0–40.0)	6.9 (2.3–26.6)	6.4 (3.5–8.9)	54.9 (4.5–130.2)	7.6 (2.7–37.1)
Diagnosis age in years n (%)					
<1	167 (54.0)	53 (60.9)	31 (79.5)	2 (50.0)	253 (57.6)
1–3	57 (18.4)	15 (17.2)	2 (5.1)	0 (0)	74 (16.9)
3–10	46 (14.9)	14 (16.1)	5 (12.8)	1 (25.0)	66 (15.0)
10–17	21 (6.8)	3 (3.4)	1 (2.6)	1 (25.0)	26 (5.9)
⩾18	18 (5.8)	2 (2.3)	0 (0)	0 (0)	20 (4.6)
Nutritional status					
WAZ at diagnosis (age 0–17 years)	**n=183**	**n=68**	**n=34**	**n=3**	**n=288**
Median (IQR)**	−1.5 (−3.2 to −0.5)	−2.8 (−4.1 to 1.6)	−4.2 (−5.3 to −3.1)	−4.0 (−4.5 to −4.0)	−2.2 (−3.8 to −0.9)
WAZ ⩽1.0 n (%)	118 (64.5)	53 (77.9)	34 (100)	3 (100)	208 (71.9)
WAZ ⩽3.0 n (%)	50 (27.3)	29 (42.6)	26 (76.5)	2 (66.7)	107 (37.2)
HAZ at diagnosis (age 0–17 years)	**n=157**	**n=45**	**n=32**	**n=2**	**n=236**
Median (IQR)**	−1.6 (−3.2 to −0.4)	−1.8 (−3.9 to −0.6)	−2.3 (−3.9 to −0.6)	−1.0 (−4.0 to −1.0)	−1.8 (−3.3 to −0.5)
HAZ ⩽1.0 n (%)	102 (65.0)	31 (68.9)	24 (75.0)	1 (50.0)	158 (66.9)
HAZ ⩽3.0 n (%)	40 (25.5)	15 (33.3)	12 (37.5)	1 (50.0)	68 (28.8)
BMI at diagnosis $kg \cdot m^{-2}$ (age ⩾18 years)	**n=6**	**n=0**	**n=0**	**n=0**	**n=6**
Median (IQR)	22.8 (18.6–24.8)	—	—	—	22.8 (18.6–24.8)
BMI<18.5 n (%)	1 (16.7)	—	—	—	1 (16.7)
Neonatal bowel obstruction n (%)	**n=315**	**n=87**	**n=41**	**n=4**	**n=447**
Yes	57 (18.1)	8 (9.2)	3 (7.3)	0 (0)	68 (15.2)
Unknown	16 (5.1)	1 (1.1)	2 (4.9)	0 (0)	19 (4.3)
Sweat-testing					
Sweat chloride $mmol \cdot L^{-1}$	**n=134**	**n=62**	**n=15**	**n=1**	**n=212**
Mean±SD	105±18	107±17	115±24	109	106±18
Sweat conductivity $mmol \cdot L^{-1}$	**n=63**	**n=21**	**n=18**	**n=0**	**n=102**
Mean±SD	104±16	110±23	105±20	—	106±19
Genotype					
p.Phe508del** n (%)	**n=315**	**n=87**	**n=41**	**n=4**	**n=447**
Homozygous	183 (58.1)	36 (29.9)	0 (0)	1 (25.0)	220 (49.2)
Heterozygous	102 (32.4)	40 (46.0)	1 (2.4)	1 (25.0)	144 (32.2)
3120+1G>A; c.2988+1G>A** n (%)	**n=315**	**n=87**	**n=41**	**n=4**	**n=447**
Homozygous	0 (0)	0 (0)	23 (56.1)	0 (0)	23 (5.1)
Heterozygous	8 (2.5)	19 (21.8)	12 (29.3)	0 (0)	39 (8.7)
Incomplete genotyping (one or two unknown *CFTR* variants) ** n (%)	18 (5.7)	19 (21.8)	12 (29.3)	0 (0)	49 (11.0)
Most common *CFTR* mutation allele frequencies[#]: alleles n (%)	**n=630**	**n=174**	**n=82**	**n=8**	**n=894**
F508del; c.1521_1523delCTT/p.Phe508del	468 (74.3)	92 (52.9)	1 (1.2)	3 (37.5)	564 (63.1)
3120+1G>A2,3; c.2988+1G>A	8 (1.3)	19 (10.9)	58 (70.7)	0 (0)	85 (9.5)
Other[¶] (<1% allele frequency)	46 (7.3)	22 (12.6)	8 (9.8)	5 (62.5)	81 (9.1)
Unknown	24 (3.8)	24 (13.8)	15 (18.3)	0 (0)	63 (7.0)
3272–26A>G1; c.3140–26A>G	15 (2.4)	8 (4.6)	0 (0)	0 (0)	23 (2.6)
394delTT1; c.262_263delTT /p.Leu881IlefsX22	18 (2.9)	0 (0)	0 (0)	0 (0)	18 (2.0)
A455E; c.1364C>A/p.Ala455Glu	11 (1.7)	5 (1.7)	0 (0)	0 (0)	16 (1.8)
N1303K1; c.3909C>G/p.Asn1303Lys	10 (1.6)	0 (0)	0 (0)	0 (0)	10 (1.1)
R553X; c.1657C>T/p.Arg553X	7 (1.1)	3 (1.7)	0 (0)	0 (0)	10 (1.1)
G542X1; c.1624G>T/p.Gly542X	9 (1.4)	0 (0)	0 (0)	0 (0)	9 (1.0)
G551D; c.1652G>A/p.Gly551Asp	8 (1.3)	1 (0.6)	0 (0)	0 (0)	9 (1.0)

WAZ: weight-for-age ; HAZ: height-for-age; BMI: body mass index. [#]Excludes 12 people for whom diagnostic criteria of the SACFR were not met; column percentages calculated with recorded number of entries as denominator value. [¶]Other *CFTR* mutations, supplementary table S1. *Indicates significance of differences in characteristic by ancestry, p<0.05; and **p<0.001.

TABLE 2 Clinical, lung function and nutritional characteristics of children and adults in the South Africa Cystic Fibrosis Registry captured in 2018[#], stratified by age

	0–6 years n=80	6–17 years =162	⩾ 18 years n=171	Total
Subjects n	**80**	**162**	**171**	**413**
Female sex n (%)	40 (50.0)	87 (53.7)	94 (55.0)	221 (53.5)
Age years	**n=80**	**n=162**	**n=171**	**n=413**
Median (IQR)	3.4 (2.1–5.0)	11.3(8.8–14.6)	26.9 (21.6–34.3)	14.7 (7.4–24.4)
Ancestry** n (%)	**n=80**	**n=162**	**n=171**	**n=413**
Caucasian	41 (51.3)	102 (63.0)	146 (85.4)	289 (70.0)
Mixed	19 (23.7)	38 (23.4)	24 (14.0)	81 (19.6)
Black African	20 (25.0)	19 (11.7)	1 (0.6)	40 (9.7)
Indian	0 (0)	3 (1.9)	0 (0)	3 (0.7)
Pancreatic insufficient n (%)	**n=80**	**n=162**	**n=171**	**n=413**
Insufficient	75 (93.8)	144 (88.9)	146 (85.4)	365 (88.4)
Socioeconomic factors				
Household cigarette smoke**n (%) exposure/smoker** n (%)	**n=80**	**n=162**	**n=171**	**n=413**
Yes	13 (16.3)	39 (24.1)	8 (4.7)	60 (14.5)
Receiving social welfare grant n (%)	**n=80**	**n=162**	**n=171**	**n=413**
Yes	15 (18.8)	31 (19.1)	19 (11.1)	65 (15.7)
Private health insurance** n (%)	**n=80**	**n=162**	**n=171**	**n=413**
Yes	40 (50.0)	86 (53.1)	116 (67.8)	242 (58.6)
Microbiology n (%)	**n=80**	**n=162**	**n=171**	**n=413**
Age in years of 1st *Pseudomonas aeruginosa*, median (IQR)	1 (0.0–2.0)	4 (1.0–8.0)	5 (1.0–17.0)	3 (1.0–9.0)
Ever had *P. aeruginosa*** n (%)	27 (33.8)	58 (35.8)	102 (59.6)	187 (45.3)
Chronic *P. aeruginosa*** n (%)				
Yes	8 (10.0)	28 (17.3)	80 (46.8)	116 (28.1)
Unknown[¶]	39 (48.8)	53 (32.7)	56 (32.7)	148 (35.8)
Chronic MSSA** n (%)				
Yes	6 (7.5)	40 (24.7)	26 (15.2)	72 (17.4)
Unknown[¶]	39 (48.8)	53 (32.7)	58 (33.9)	150 (36.3)
Ever had MRSA n (%)	2 (2.5)	15 (9.3)	9 (5.3)	26 (6.3)
Chronic MRSA* n (%)				
Yes	0 (0)	7 (4.3)	7 (4.1)	14 (3.4)
Unknown[¶]	38 (47.5)	52 (32.1)	59 (34.5)	149 (36.1)
Chronic *Burkholderia cepacia** n (%)				
Yes	0 (0)	5 (3.1)	8 (4.7)	13 (3.1)
Unknown[¶]	38 (47.5)	52 (32.1)	61 (35.7)	151 (36.6)
Chronic *Aspergillus* spp.* n (%)				
Yes	0 (0)	15 (9.3)	14 (8.2)	29 (7.0)
Unknown[¶]	37 (46.3)	52 (32.1)	58 (33.9)	147 (35.6)
Chronic *Haemophilus influenzae** n (%)				
Yes	1 (1.3)	4 (2.5)	1 (0.6)	6 (1.5)
Unknown[¶]	39 (48.8)	54 (33.3)	60 (35.1)	153 (37.0)
Another fungus/mould* n (%)	12 (15.0)	26 (16.0)	45 (26.3)	83 (20.1)
Any NTM isolate n (%)	0 (0)	2 (1.2)	3 (1.8)	5 (1.2)
Pulmonary therapies n (%) (>3 months continuous)	**n=80**	**n=162**	**n=171**	**n=413**
Inhaled hypertonic saline	45 (56.3)	85 (52.5)	79 (46.2)	209 (50.6)
Recombinant DNase**	9 (11.3)	40 (24.7)	71 (41.5)	120 (29.1)
Inhaled antibiotics**	31 (38.8)	71 (43.8)	120 (70.2)	222 (53.8)
Low-dose azithromycin**	47 (58.8)	127 (78.4)	153 (89.5)	327 (79.2)
Complications/comorbidity n (%)	**n=80**	**n=162**	**n=171**	**n=413**
ABPA	0 (0)	8 (4.9)	10 (5.8)	18 (4.4)
CF-related diabetes	0 (0)	9 (5.6)	53 (31.0)	62 (15.0)
CF-related liver disease*				
With cirrhosis[+]	2 (2.5)	11 (6.8)	10 (5.8)	23 (5.6)
Without cirrhosis	5 (6.3)	29 (17.9)	29 (17.0)	63 (15.3)
Pneumothorax	0 (0)	1 (0.6)	1 (0.6)	2 (0.5)
Haemoptysis major (>250 mL)	1 (1.3)	5 (3.1)	1 (0.6)	7 (1.7)
Occurrence of malignancy	0 (0)	0 (0)	2 (1.2)	2 (0.5)
Nutritional status				
WHZ (current age 0–2 years)	**n=16**	—	—	**n=16**

Continued

TABLE 2 Continued

	0–6 years n=80	6–17 years =162	⩾ 18 years n=171	Total
Median (IQR)	−0.6 (−1.4–1.2)	—	—	−0.6 (−1.4–1.2)
WHZ ⩽1	7 (43.8)	—	—	7 (43.8)
BMIZ (current age 2–17 years)	**n=60**	**n=161**	—	**n=221**
Median (IQR)	0.4 (−0.4–1.1)	−0.5 (−1.1–0.4)	—	−0.3 (−1.0–0.6)
BMIZ ⩽1	6 (10.0)	50 (31.1)	—	56 (25.3)
BMI kg·m^{-2} (age ⩾18 years)			**n=161**	**n=161**
Median (IQR)			21.2 (19.2– 23.8)	21.2 (19.2–23.8)
Undernutrition[§,*] n (%)	**n=76**	**n=161**	**n=161**	**n=398**
Yes	13 (17.1)	50 (31.1)	28 (17.4)	91 (22.9)
Lung function	—	**n= 140**	**n= 152**	**n= 292**
FEV_1 % pred** n (%)				
>70	—	107 (76.4)	62 (40.8)	169 (57.9)
40–70	—	30 (21.4)	67 (44.1)	97 (33.2)
<40	—	3 (2.1)	23 (15.1)	26 (8.9)
FEV_1 % pred** median (IQR)	—	87.2 (71.3–102.0)	64.6 (50.1–83.1)	77.4 (58.1–91.8)
FEV_1z n (%)	—			
⩽ −1.0; ⩾2.0	—	30 (21.4)	25 (16.4)	55 (18.8)
⩽ −2.0; ⩾3.0	—	15 (10.7)	28 (18.4)	43 (14.7)
⩽ −3.0	—	26 (18.6)	70 (46.1)	96 (32.9)
FEV_1z ** median (IQR)	—	−1.0 (−2.4–0.1)	−2.8 (−4.0– −1.4)	−1.9 (−3.4–0.7)

BMIZ: body mass index z-score; WHZ: weight-for-height z-score; NTM: non-tuberculous mycobacterium; FEV_1z: forced expiratory volume in 1 s z-score; FEV_1 % pred: forced expiratory volume in 1 s per cent predicted; ABPA: allergic bronchopulmonary aspergillosis; CF: cystic fibrosis; MSSA: methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*. [#]Excludes 20 not seen in 2018, 2 with previous liver transplants and 12 with previous lung transplants. [¶]Unknown: Chronic pulmonary infection status was classified as unknown if less than four respiratory samples were submitted for culture during the year or the infection status of each pathogen could not be established from past medical records. [+]Includes liver cirrhosis with portal hypertension. [§]Undernutrition definition: World Health Organization (WHO) nutritional reference equation WHZ ⩽1 SD in children <2 years of age; BMI z-score (BMI kg·m^{-2}) ⩽1.0 children aged 2–17 years; and BMI <18.5 kg·m^{-2} in adults ⩾18 years of age. *Indicates significance of differences in characteristic by age group, p<0.05; and **p<0.001.

one sweat conductivity test was documented in 212 (47%) and 102 (24%) people, respectively. One hundred and fifty-two (34%) people did not have any sweat tests documented. Reasons for missing sweat test were not documented in the SACFR but include either not done or results missing from medical records.

Complete genotype diagnosis was available in 398 (89%): p.Phe508del was the most common *CFTR* variant identified in homozygous (49.2%) or heterozygous (32.2%) state. 3120+1GA was the second most common *CFTR* variant: 23 (5.1%) in homozygous and 39 (8.7%) in heterozygous state, each mostly in non-Caucasians (p<0.001); with 56.1% black Africans homozygous for 3120+1GA. Incomplete genotyping (one or two unknown *CFTR* variants) differed significantly by ancestry (p<0.001) with greater prevalence among those of mixed ancestry (21.8%) and black Africans (29.3%) compared to Caucasians (5.7%) (table 1).

General description of SACFR cohort in 2018 (n=413)

Twenty people not seen in 2018 for follow-up, 10 lung transplant (three in 2018) and two liver transplant recipients were excluded from analysis. The median age of the SACFR cohort in 2018 was 14.7 years (IQR 7.4–24.4), with 242 out of 413 (58.6%) children younger than 18 years of age. There were more non-Caucasian children (n=99, 40.9%) compared to adults (n=25, 14.6%) (p<0.001). Except for one, all black Africans (n=39) were <18 years old. One hundred and seventy-one (41.4%) people received care exclusively in the public health sector and 242 (58.6%) received care partially or exclusively in the private health sector. Human immunodeficiency virus testing was documented in 202 (45.2%) of which one adolescent was HIV-infected and three children were HIV-exposed, uninfected. There were three reported deaths in 2018, all in adults. Demographic, socioeconomic, nutritional, microbiological and comorbidity/complication details are presented in table 2.

Lung function and correlates of SLD in 2018

Lung function measurements from 2018 were available in 292 individuals (140 children ⩾6 years and 152 adults; no LF documented n=41) (table 2). The distribution of LF across age categories is shown in figure 1 with significant differences by age (p<0.001) and a clear trend of decreasing FEV_1 % pred with

TABLE 3 Unadjusted and adjusted associations with severe lung disease in children⩾6 years and adults in the South Africa Cystic Fibrosis Registry, 2018

	Severe lung disease of FEV_1z ⩽3.0 (n=292)				
	Univariable analysis[#]			Multivariable analysis (n=190)	
	n	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Neonatal bowel obstruction (ref: no)	275	0.58 (0.28–1.19)	0.126	NS	
Age diagnosis (units: 10 years)	285	1.26 (0.90–1.76)	0.180	NS	
Current age (units: 10 years)	292	1.99 (1.55–2.54)	<0.001*	2.23 (1.50–3.31)	<0.001
p.Phe508del (ref: neither record)					
Homozygous	292	0.77 (0.37–1.57)	0.069	NS	
Heterozygous	292	1.45 (0.70–3.01)			
Caucasian (ref: other ancestry)	292	1.50 (0.83–2.72)	0.171	NS	
Ever had *P. aeruginosa* (ref: no)	279	4.36 (1.65–11.49)	0.001*	1.66 (0.34–8.12)	0.529
Time since first *P. aeruginosa* isolate (per 10-year interval)[¶]	133	2.12 (1.38–3.25)	<0.001*	1.25 (0.85–1.84)	0.259
Chronic *P. aeruginosa* (ref: no)	201	3.81 (2.08–6.95)	<0.001*	1.98 (0.90–4.34)	0.088
Chronic MSSA (ref: no)	198	0.57 (0.30–1.10)	0.089	NS	
Ever had MRSA (ref: no)	261	2.46 (0.98–6.18)	0.055	NS	
Chronic MRSA (ref: no)	198	8.88 (1.89–41.73)	0.001*	16.75 (1.74–161.50)	0.015
Other fungus or mould (ref: no)	292	2.19 (1.22–3.93)	<0.009*	1.31 (0.58–2.93)	0.518
ABPA (ref: no)	261	0.29 (0.06–1.30)	0.064	NS	
Household cigarette smoke exposure/ smoker (ref: no)	292	0.62 (0.30–1.28)	0.181	NS	
CF-related diabetes (ref: no)	286	3.79 (2.10–6.84)	<0.001*	1.03 (0.46–2.33)	0.939
CF-liver disease with cirrhosis (ref: no)	282	2.87 (1.15–7.14)	0.073	NS	
Undernutrition[+] (ref: no)	292	3.16 (1.72–5.83)	<0.001*	5.20 (2.23–12.13)	<0.001

FEV_1z: forced expiratory volume in 1 s z-score; MSSA: methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*; ABPA: allergic bronchopulmonary aspergillosis; CF: cystic fibrosis; WHZ: weight-for-height z-score; BMIZ: body mass index z-score. Severe lung disease: FEV_1z ⩽3 in children ⩾6 years. [#]All variables with unadjusted p-values <0.2 in the univariable analyses are tabulated. Refer to supplementary table S3 for full set of univariable results. [¶]Included as an interaction term, to apply only to those who have ever had *P. aeruginosa*. [+]Undernutrition includes: WHZ ⩽1.0, <2 years of age; BMIZ ⩽1.0, 2–17 years; or BMI <18.5 $kg \cdot m^{-2}$, ⩾18 years. *Unadjusted p-values are shown; indicated variables had adjusted p-values <0.2 using Holm's method and were thus included in the multivariable regression model.

TABLE 4 Unadjusted and adjusted associations with undernutrition in children and adults in the South Africa Cystic Fibrosis Registry, 2018

	Undernutrition[#] (n=398)				
	Univariable analysis[¶]			Multivariable analysis (n=190)	
	n	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
WAZ ⩽1.0 at diagnosis (ref: ⩾−1)	270	2.18 (1.07–4.44)	0.024*	Excluded to preserve n due to large % missing	
Current age (unit: 10 years)	398	0.82 (0.66–1.01)	0.062	0.96 (0.76–1.21)	0.698
P.Phe508del (ref neither record)					
Homozygous	398	0.50 (0.27–0.92)	0.043	NS	
Heterozygous	398	0.85 (0.46–1.58)			
3120+1G>A hetero/homozygous	398	2.55 (1.42–4.58)	0.002*	1.32 (0.66–2.68)	0.438
Caucasian (ref: other ancestry)	398	0.35 (0.22–0.57)	<0.001*	0.56 (0.28–1.12)	0.100
Receiving social welfare grant (ref: no)	398	2.99 (1.70–5.25)	<0.001*	1.81 (0.92–3.57)	0.088
Private health insurance (ref: no)	398	0.46 (0.28–0.73)	<0.001*	0.87 (0.46–1.63)	0.661
Ever had MRSA (ref: no)	351	1.86 (0.80–4.35)	0.165	NS	
Chronic MRSA (ref: no)	255	2.31 (0.77–6.94)	0.145	NS	
Chronic *P. aeruginosa* (ref: no)	256	1.76 (1.00–3.12)	0.050	NS	

NS: nonsignificant; WAZ: weight-for-age; MRSA: methicillin-resistant *S. aureus*; WHZ: weight-for-height z-score; BMIZ: body mass index z-score. [#]Undernutrition includes: WHZ ⩽1.0, <2 years age; BMIZ ⩽1.0, 2–17 years; or BMI<18.5 $kg \cdot m^{-2}$, ⩾18 years. [¶]All variables with unadjusted p-values <0.2 in the univariable analyses are tabulated. Refer to supplementary table S4 for full set of univariable results. *Unadjusted p-values are shown; indicated variables had adjusted p-values<0.2 using Holm's method and were thus included in the multivariable regression model.

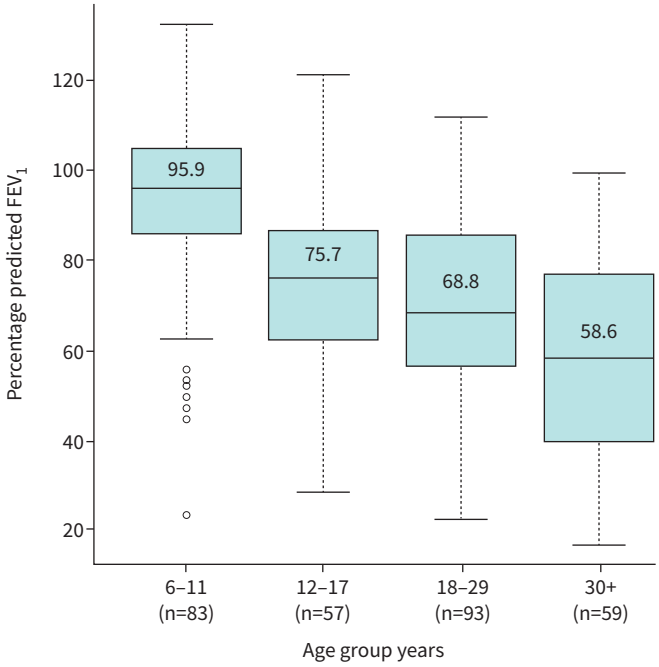

FIGURE 1 Forced expiratory volume in 1 s (FEV_1) per cent predicted by age category in adults and children ⩾6 years in South Africa Cystic Fibrosis Registry, 2018. Boxes indicate first to third quartiles, the dividing line the median, whiskers the remaining points up to length 1.5 times the interquartile range and markers any remaining outliers.

increasing age, and largest observed decline in median FEV_1% pred between 6–11 years (95.9% pred) and 12–17 years (75.7% pred) age groups.

As expected, there were significant differences between the age groups 0–6 years, 6–17 years and ⩾18 years for the majority of microbiology cultures and pulmonary therapies (table 2). Comparison between children aged 6–17 years and adults ⩾18 years showed that ever had *P. aeruginosa* (p<0.001), and chronic *P. aeruginosa* infection (p<0.001) and isolation of fungus or mould species (p=0.015) was more prevalent in adults. Isolation of any non-tuberculous mycobacteria (NTM, 1.2%) and chronic MRSA infection (6.3%) was uncommon in all ages; one child had confirmed *M. tuberculosis* infection. Classification of "chronic infection" status for multiple pathogens was not possible in approximately one third of individuals due to insufficient number of sputum samples collected in the year of follow-up. Most individuals ⩾6 years were receiving low-dose azithromycin 280 (84.1%); inhaled antibiotics 191 (57.4%); inhaled hypertonic saline 164 (49.2%) and recombinant DNase 111 (33.3%).

BMI was associated with LF, as shown in figure 2. There were significantly positive correlations between BMI z-scores and FEV_1 z-scores in children aged 6–17 years (Pearson correlation coefficient 0.39; 95% CI 0.24–0.52; p<0.001) and between BMI ($kg \cdot m^{-2}$) and FEV_1 z-scores in adults aged ⩾18 years (0.28; 95% CI 0.13–0.42; p<0.001).

Twenty-six (18.6%) children and 70 adults (46.1%) had study-defined SLD, of which two children (2.1%) and 23 adults (15.1%) had FEV_1 <40% pred. No evidence of association was observed with SLD and receiving inhaled hypertonic saline (p=0.256) or recombinant DNase (p=0.742). Conversely, low-dose azithromycin (98% *versus* 79%; p<0.01) and inhaled antibiotic therapies (75.5% *versus* 51.4%; p< 0.01) were prescribed more frequently in individuals with SLD than without SLD.

Univariable (p<0.2) and adjusted multivariable associations with SLD are presented in table 3. Older age (aOR 2.23 per 10-year units: 95% CI 1.50–3.31) and undernutrition (aOR 5.20; 95% CI 2.23–12.13) were independently associated with SLD, as was chronic MRSA infection (aOR 16.75; 95% CI 1.74–161.50) although there is substantial uncertainty in magnitude of the association. Chronic *P. aeruginosa* infection was associated with SLD, but the effect was not significant (aOR 1.98; 95% CI 0.90–4.34) after adjusting for other variables (table 3).

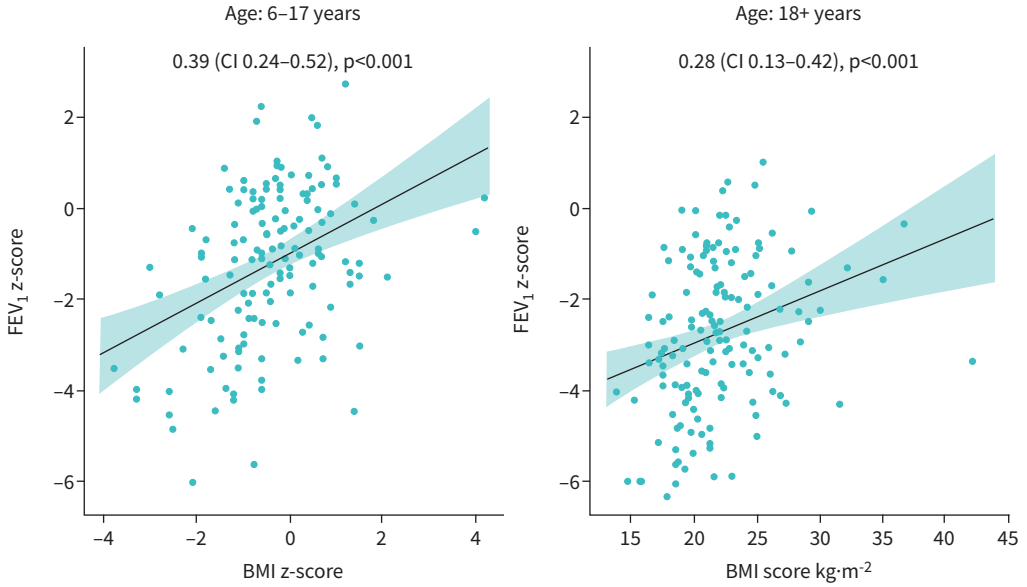

FIGURE 2 Scatter plot of forced expiratory volume in 1 s (FEV_1) z-scores *versus* body mass index (BMI) z-scores (children aged <18 years) or BMI measurements (adults aged ⩾18 years) in South Africa Cystic Fibrosis Registry, 2018, with Pearson correlation coefficients indicated.

Nutrition in 2018

Nutritional measurements from 2018 were available in 237 children and 161 adults, of which the majority (354, 88.9%) were pancreatic insufficient. Overall, study-defined undernutrition was present in 63 (26.6%) children and 28 (17.4%) adults.

On univariable analysis, undernutrition was associated with low WAZ at diagnosis, non-Caucasian ethnicity, 3120+1G>A genotype, chronic *P. aeruginosa* infection and indicators of low-SES: receiving public healthcare and a social welfare grant (table 4). While receiving a social welfare grant tended towards statistical significance (aOR 1.81; 95% CI 0.92–3.57), multivariable analysis did not identify any independent associations with undernutrition.

Discussion

This first comprehensive description of CF in SA highlights the importance and value of a CF registry in understanding the unique spectrum and epidemiology of CF in LMIC such as SA. Our findings highlight several important aspects which have diagnostic and therapeutic implications for future CF care in SA and other LMICs. These include ethnic-specific genotypes, limitations in areas of CF diagnosis and care, and correlating nutrition and LF outcomes. Furthermore, the higher proportion of children compared to adults, similarly observed in other LMIC such as Brazil, may be the effect of lower survival age in SA compared to high-income countries where adults outnumber children [11]. The newly established SACFR is therefore a useful tool in the long term to prioritise and guide interventions that could improve CF outcomes in SA where median survival age in 2008 at a single centre was below 20 years of age [28].

The true number of people living with CF in SA is unknown. Based on *CFTR* carrier frequency rates of studies dating back to 1999, estimates of CF incidence in Caucasian, mixed race and black African populations are 1 in 3000 (carrier frequency 1 in 23), 1 in 10 300 (carrier frequency 1 in 55) and 1 in 784–13 924 (carrier frequency 1 in 14 to 1 in 59 live births), respectively [18, 29]. A national survey in 2016 reported nearly 56 million people in SA, of which the majority (45 million) were black Africans and 4.5 million Caucasian [30]. By extrapolation, the estimated number of children born with CF in the same generation would have been 3214 black Africans and 1500 Caucasians. There appears to be a significant discrepancy in population estimates and documented number of people with CF in all ancestries, especially black Africans. Early reports of CF in black Africans in SA and Kenya date back to 1959 [31, 32]. Since then, more studies from SA, Rwanda and Sudan have described CF in children of African ancestry with the 3120+1G>A mutation [18, 33–37]. It is notable that all, but one, black Africans with CF in the SACFR are children. This may be explained in our opinion by increased awareness and diagnosis of CF in

non-Caucasian people in the last decade or increased mortality in non-Caucasians before CF is diagnosed and represents an area of future research that stems from the SACFR. Cystic fibrosis expertise and diagnosis capacity are located only in a few cities across SA. It is likely that there are some people receiving care outside recognised CF care centres or practices that have not been captured in the SACFR. Furthermore, fragmented healthcare systems and lack of diagnostic capacity in under-resourced rural provinces are factors in our experience that contribute to delayed or missed CF diagnosis in children in SA. Increased CF-related infant mortality and malnutrition in children from lower socioeconomic groups has been previously documented in SA [28, 37]. In the absence of newborn screening, we suspect high numbers of undocumented CF-related infant deaths may be occurring in SA and incorrectly attributed to malnutrition or infectious disease, which is common in poor and rural communities. The high proportion (37%) of children in our study with severe malnutrition at the time of CF diagnosis is supportive of this hypothesis.

As expected, the genotype profile of CF in SA is closely linked to ancestry (table 1 and supplementary table S1). p.Phe508del is the most common mutation in Caucasians and people with mixed ancestry. Approximately 80% of people with CF in SA have at least one copy of p.Phe508del mutation and are therefore eligible for triple combination (elexacaftor/ivacaftor/tezacaftor) CFTR modulator therapy. In contrast, 3120+1G>A, a class 1 minimal function mutation, was the second most common mutation in people with mixed ancestry and the most common mutation in black Africans. Importantly, incomplete or unknown genotyping was present in 11% of people, with higher prevalence observed in people with mixed ancestry and black Africans. Similar genotype profiles and increased prevalence of rare or unknown *CFTR* mutations has been reported in Brazil, a LMIC which shares demographic and socioeconomic characteristics with SA [38]. These findings highlight the limitation of commercial *CFTR* testing kits, which are more suited for people of European descent, and the need for LMIC to develop and adopt genotyping strategies that are more appropriate for local populations. Rare, unknown and 3120+1G>A collectively comprise nearly a third of all alleles in the SACFR population. This has implications for diagnostic strategies including newborn screening and highlights the importance of the sweat test to confirm CF diagnosis in LMIC where availability of full *CFTR* genotyping and next generation sequencing is often limited or absent and may lead to a diagnosis of CF being unconfirmed or missed. Of concern, only half of registry entries had at least one sweat chloride/sweat conductivity test documented. Furthermore, sweat conductivity was sometimes the only sweat test reported. Although sweat conductivity has been validated to diagnose CF associated with minimal function *CFTR* mutations, interpretation of intermediate conductivity reference ranges is problematic, and the utility of sweat conductivity in diagnosing atypical CF or CF-related disorders is unknown [39]. The high number of missing sweat test results in the SACFR in our opinion is explained by either lack of access to sweat-testing outside the main cities and missing results from medical records, especially in older patients. Improving documentation and accessibility to sweat chloride testing in SA is highlighted through this study as an important priority. Another implication of our findings is recognition that most black Africans, owing to the high prevalence of the 3120+1G>A mutation, will not benefit from currently licensed CFTR modulator therapies. Advocacy to include African people in global *CFTR* modulator drug development initiatives is another priority.

Poor LF and nutrition are important co-dependent predictors of survival in CF [8]. Identifying modifiable factors that preserve LF decline and improve nutrition is key to improving CF survival. After adjusting for age and factors associated with poor LF that were identified in univariable analyses, undernutrition was the strongest independent modifiable factor associated with SLD. These findings mirror differences observed with LF, nutrition and survival outcomes in Canada compared to the US. Better outcomes in Canada have been attributed to differences in childhood nutrition, access to universal free CF care and access to lung transplantation. However, LF and nutrition outcomes in the US are improving, which is attributed to introduction in the US of high-fat, high-calorie diets, newborn screening and improved access to CF healthcare [8, 40]. Interventions that improve CF nutrition, particularly amongst poor communities in public healthcare services in SA where undernutrition is most prevalent, are therefore key to improving CF survival in SA. Newborn screening for hereditary conditions including CF is available only on request in the private sector and for a fee to the public, and therefore rarely performed in SA. This presents a significant barrier to improving CF outcomes in SA, especially severe malnutrition, as reported in this study, is common in SA at the time of diagnosis. Chronic *P. aeruginosa* and MRSA infections are additional modifiable factors associated with lower LF in SA, which is consistent with international observations [6]. Inhaled antibiotic therapies (*e.g.* tobramycin, aztreonam) and dry powder antibiotic formulations are either not available or very expensive relative to household income in SA. The average disposable household income per annum in SA is approximately 2300 USD [41]. The cost of 1 month of rDNAse and tobramycin inhalation solution is approximately 3- and 10-fold the average monthly

household income, respectively. Active surveillance to detect early infections and aggressive eradication protocols using effective low-cost alternate approaches such as inhalation of gentamycin intravenous solution for *P. aeruginosa* eradication can be more widely adopted throughout SA [42]. Our LF data must, however, be interpreted with caution owing to the small number of individuals with chronic MRSA and up to a third of people with missing chronic lung infection status data because of insufficient sputum samples collected during the year of review or infrequent clinic visits. This highlights another important deficit in SA CF care needing attention. The SACFR adopted European CF registry chronic infection status definitions in line with international CF registry harmonisation guidelines [20]. In our experience, factors preventing frequent sputum sampling practices in SA include fragmented health services, limited access to multidisciplinary CF care and financial constraints in people with limited or no private health insurance who need to pay out of pocket for surveillance or routine laboratory investigations.

Interpretation of the SACFR data is limited by the absence of longitudinal or retrospective data which has excluded CF-related outcomes and deaths prior to 2018, children who may have died of CF without being diagnosed or people in whom informed consent for inclusion in the registry was not yet obtained. Longitudinal cohort data captured in future by the SACFR will be helpful to establish early life determinants of LF and CF survival in South Africa. Although we estimate most people alive and diagnosed with CF are captured in the SACFR, we suspect there are still a small number of CF patients receiving care outside the recognised participating SACFR clinics and practices. In addition, several patients were excluded from the LF and nutrition analyses due to missing data, which is an inherent challenge with registry data collection and analysis. Missing SACFR data is a major limitation of this study as data entry into the registry relies on relevant measurements and investigations being accurately recorded in the medical records by treating clinicians. Routine CF care and frequency of CF visits is unregulated and not standardised in SA. Private sector care is strongly influenced by individual patient financial resources and variable levels of reimbursement by private health insurers. Public sector care, which serves predominantly uninsured poorer patients, is inconsistent at different clinics and frequency of routine attendance at CF clinics is dependent on access to reliable transport and other socioeconomic factors. People with CF living in remote or rural areas infrequently attend participating CF clinics, which could be another factor contributing to missing data. Missing data or incomplete information relating to CF diagnosis in older children and adults was an additional limitation.

In summary, this first comprehensive overview of CF in SA has identified important epidemiological data which are useful to guide strategies and interventions to improve CF diagnosis capacity and CF-related outcomes. Based on genotype, most people with CF in SA are eligible for highly effective CFTR modulator therapy which is currently not available in SA. Accelerating affordable access to CFTR modulator therapy and improving nutrition and treatment of MRSA and *P. aeruginosa* infections will lead to better LF outcomes in SA.

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References

1 Annual CFF Registry Report 2018. www.cff.org/Research/Researcher-Resources/Patient-Registry/2018-Patient-Registry-Annual-Data-Report.pdf Date last accessed: 19 September 2020.
2 Corriveau S, Sykes J, Stephenson AL. Cystic fibrosis survival: the changing epidemiology. *Curr Opin Pulm Med* 2018; 24: 574–578.
3 McColley SA, Schechter MS, Morgan WJ, *et al.* Risk factors for mortality before age 18 years in cystic fibrosis. *Pediatr Pulmonol* 2017; 52: 909–915.
4 Fink AK, Loeffler DR, Marshall BC, *et al.* Data that empower: the success and promise of CF patient registries. *Pediatr Pulmonol* 2017; 52: S44–s51.
5 Jackson AD, Goss CH. Epidemiology of CF: how registries can be used to advance our understanding of the CF population. *J Cyst Fibros* 2018; 17: 297–305.
6 Harun SN, Wainwright C, Klein K, *et al.* A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis. *Paediatr Respir Rev* 2016; 20: 55–66.
7 Loukou I, Moustaki M, Sardeli O, *et al.* Association of vitamin D status with lung function measurements in children and adolescents with cystic fibrosis. *Pediatr Pulmonol* 2020; 55: 1375–1380.
8 Goss CH, Sykes J, Stanojevic S, *et al.* Comparison of nutrition and lung function outcomes in patients with cystic fibrosis living in Canada and the United States. *Am J Respir Crit Care Med* 2018; 197: 768–775.
9 Crowley EM, Bosslet GT, Khan B, *et al.* Social complexity negatively influences lung function in cystic fibrosis after transfer to adult care. *Pediatr Pulmonol* 2020; 55: 24–26.
10 Taylor-Robinson DC, Smyth RL, Diggle PJ, *et al.* The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study. *Lancet Respir Med* 2013; 1: 121–128.
11 da Silva LVRF, Zampoli M, Cohen-Cymberknoh M, *et al.* Cystic fibrosis in low and middle-income countries (LMIC): a view from four different regions of the world; Published ahead of print. accessed 20 September 2020. *Paediatr Respir Rev* 2020; in press [doi:10.1016/j.prrv.2020.07.004.]
12 McGarry ME, Neuhaus JM, Nielson DW, *et al.* Regional variations in longitudinal pulmonary function: a comparison of Hispanic and non-Hispanic subjects with cystic fibrosis in the United States. *Pediatr Pulmonol* 2019; 54: 1382–1390.
13 Rho J, Ahn C, Gao A, *et al.* Disparities in mortality of Hispanic patients with cystic fibrosis in the United States. A National and Regional Cohort Study. *Am J Respir Crit Care Med* 2018; 198: 1055–1063.
14 Francis D, Webster E. Poverty and inequality in South Africa: critical reflections. *Development Southern Africa* 2019; 36: 788–802.
15 Zampoli M. Cystic fibrosis: what's new in South Africa in 2019. *S Afr Med J* 2019; 109: 16–19.
16 Worldometer. www.worldometers.info/world-population/south-africa-population/ Date last accessed: 25 April 2020.
17 Goldman A, Graf C, Ramsay M, *et al.* Molecular diagnosis of cystic fibrosis in South African populations. *S Afr Med J* 2003; 93: 518–519.
18 Padoa C, Goldman A, Jenkins T, *et al.* Cystic fibrosis carrier frequencies in populations of African origin. *J Med Genet* 1999; 36: 41–44.
19 Stewart C, Pepper MS. Cystic fibrosis on the African continent. *Genet Med* 2016; 18: 653–662.
20 ECFS Patient Registry Annual Data Report 2017. www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report2017_v1.3.pdf Date last: accessed 10 January 2021.
21 Zampoli M, Verstraete J, Frauendorf M, *et al.* South African Cystic Fibrosis Patient Registry Annual Report 2018. www.sacfa.org.za/wp-content/uploads/SA-CF-RegistryFullReport2018.pdf Date last accessed: 10 January 2021.
22 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
23 Quanjer PH, Pretto JJ, Brazzale DJ, *et al.* Grading the severity of airways obstruction: new wine in new bottles. *Eur Respir J* 2014; 43: 505–512.
24 CFTR2. https://cftr2.org/. accessed 25/04/2020.

25 Farrell PM, White TB, Ren CL, *et al.* Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr* 2017; 181s: S4–S15. e11.

26 Lee TWR, Brownlee KG, Conway SP, *et al.* Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. *J Cyst Fibros* 2003; 2: 29–34.

27 SACFA. The South African Cystic Fibrosis Consensus Guidelines, 5th Edition, 2017. www.sacfa.org.za/wp-content/uploads/2017_09_14_CF_Consensus_Guidelines_2017.pdf Date last accessed: 20 September 2020.

28 Westwood A. *The prognosis of cystic fibrosis in the Western Cape province of South Africa: a 33 year study*. Doctor of Medicine thesis, University of Cape Town, 2008.

29 Westwood T, Henderson B, Ramsay M. Diagnosing cystic fibrosis in South Africa. *S Afr Med J* 2006; 96: 304–30306.

30 Statistics South Africa. Community Survey 2016 report media release, 30 June 2016. www.statssa.gov.za/?p=7957&gclid=CjwKCAjwkoz7BRBPEiwAeKw3q8IbwTUHmYR6Ub5OTeLgP_xPESMJPm2g1GrjUeqtj-Plg-V281tPShoCiKoQAvD_BwE Date last accessed: 18 September 2020.

31 Macdougall L. Fibrocystic disease of the pancreas in African children. *The Lancet* 1962; 280: 409–410.

32 Levin SE, Blumberg H, Zamit R, *et al.* Mucoviscidosis (cystic fibrosis of the pancreas) in Bantu twin neonates. *S Afr Med J* 1967; 41: 482–485.

33 Masekela R, Zampoli M, Westwood AT, *et al.* Phenotypic expression of the 3120+1G>A mutation in non-Caucasian children with cystic fibrosis in South Africa. *J Cyst Fibros* 2013; 12: 363–366.

34 Ibrahim SA, Fadl Elmola MA, Karrar ZA, *et al.* Cystic fibrosis in Sudanese children: first report of 35 cases. *Sudan J Paediatr* 2014; 14: 39–44.

35 Mutesa L, Azad AK, Verhaeghe C, *et al.* Genetic analysis of Rwandan patients with cystic fibrosis-like symptoms: identification of novel cystic fibrosis transmembrane conductance regulator and epithelial sodium channel gene variants. *Chest* 2009; 135: 1233–1242.

36 Westwood T, Brown R. Cystic fibrosis in black patients: Western Cape experiences. *S Afr Med J* 2006; 96: 288–289.

37 Owusu SK, Morrow BM, White D, *et al.* Cystic fibrosis in black African children in South Africa: a case control study. *J Cyst Fibros* 2020; 19: 540–545.

38 da Silva LVRF, Maróstica PJC, Athanazio RA, *et al.* Extensive CFTR sequencing through NGS in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies in the country. *J Cyst Fibros*; in press [doi:101016/jjcf202008007].

39 Mattar AC, Leone C, Rodrigues JC, *et al.* Sweat conductivity: an accurate diagnostic test for cystic fibrosis? *J Cyst Fibros* 2014; 13: 528–533.

40 Stephenson AL, Sykes J, Stanojevic S, *et al.* Survival comparison of patients with cystic fibrosis in Canada and the United States: a population-based cohort study. *Ann Intern Med* 2017; 166: 537–546.

41 Statista Research Department. Household disposable income in South Africa from 1990 to 2019. www.statista.com/statistics/874035/household-disposable-income-in-south-africa/#:~:text=In%202019%2C%20South%20African%20households,about%2034%2C037%20South%20African%20Rand Date last accessed: 8 May 2021.

42 Van Stormbroek B, Zampoli M, Morrow BM. Nebulized gentamicin in combination with systemic antibiotics for eradicating early *Pseudomonas aeruginosa* infection in children with cystic fibrosis. *Pediatr Pulmonol* 2019; 54: 393–398.